PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

Applicant(s): Nobuto YAMAMOTO

Serial No: 09/826,463 | Group Art Unit: 1647

Filed: April 5, 2001 | Examiner: David S. ROMEO

Att. Docket No.: Y1004/20017 | Confirmation No.: 2419

For: PREPARATION OF POTENT MACROPHAGE ACTIVATING FACTORS DERIVED FROM CLONED VITAMIN D BINDING PROTEIN AND ITS DOMAIN AND THEIR THERAPEUTIC USAGE FOR CANCER, HIV-INFECTION AND OSTEOPETROSIS

APPEAL BRIEF UNDER 37 CFR § 1.192

Mail Stop Appeal Brief -- Patents
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Sir:

Introduction

Further to the Notice of Appeal filed August 29, 2006 in response to the Final Rejection in which claims 22 and 24 were finally rejected, and the Pre-Appeal Brief Conference Decision of October 11, 2006, Appellant respectfully requests reversal of the Final Rejection and allowance of the claims.

I. Real Party in Interest

The real party in interest for this appeal and the present application is the inventor.

II. Related Appeals and Interferences

There are presently no pending appeals or interferences, known to appellant, appellant's representatives or the assignee, that would directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. Status of Claims

Claims 22 and 24 are pending.

Claims 1-21 and 23 are canceled

Claims 22 and 24 stand rejected and Appellant appeals the rejection of these claims.

A copy of the rejected claims involved in the present appeal is provided in the Claims Appendix (Section IX).

IV. Status of Amendments

No amendments have been filed after the appealed Final Rejection dated May 1, 2006. Appellant believes that no outstanding amendments exist.

V. Summary of Claimed Subject Matter

The claimed invention relates to potent macrophage activating factors, prepared by oligosaccharide digestion of the cloned vitamin D binding protein (Gc protein), useful for treating cancer, HIV-infection and osteopetrosis, and as adjuvants for immunization and vaccination. Full length cDNA encoding the human Gc protein was isolated from a human liver cDNA library and cloned into the baculoviral expression system in the insect cells. This system uses many of the protein modification and processing reactions, such as glycosylation, present in higher eukaryotic cells and produces a large amount of cloned Gc protein. The cloned Gc protein treated with immobilized β-galactosidase and sialidase results in a cloned macrophage activating factor (GcMAFc). Incubation of macrophages with GcMAFc resulted in a 5-fold increased phagocytic and a 15-fold increase in the superoxide generating capacity of

macrophages.

Independent **claim 22** is drawn to a process for producing a cloned macrophage activating factor (GcMAFc) (Specification at page 15, lines 8-14), comprising cloning Gc1 isoform into a baculovirus vector (Specification at page 12, lines 14-22), expressing the cloned Gc1 isoform (Specification at page 15, lines 8-14), producing a Gc1 protein (see Figure 3), contacting the cloned Gc1 protein with immobilized β-galactosidase and sialidase (Specification at page 15, lines 8-14), and obtaining the cloned GcMAFc (Specification at page 15, lines 8-14).

Independent **claim 24** is drawn to a process for producing a cloned macrophage activating factor (GcMAFc) (Specification at page 15, lines 8-14), comprising cloning Gc1 isoform into a baculovirus vector (Specification at page 12, lines 14-22), expressing the cloned Gc1 isoform (Specification at page 15, lines 8-14), producing a Gc1 protein (see Figure 3), sequencing the cloned Gc1 peptide and confirming it is a wild type Gc1 protein (Specification at page 10, lines 4-11), contacting the cloned Gc1 protein with immobilized β-galactosidase and sialidase (Specification at page 15, lines 8-14), and obtaining the cloned GcMAFc (Specification at page 15, lines 8-14).

VI. Grounds of Rejection to be Reviewed on Appeal

Issue I. Whether claim 24 was properly rejected under 35 USC § 112 first paragraph as containing new matter.

Issue II. Whether claim 22 was properly rejected under 35 USC § 103(a) as being obvious over U.S. Patent No. 5,177,002 (Yamamoto) in view of Cooke (1985), Quirk (1989), U.S. Patent No. 5,652,352 (Lichenstein), U.S. Patent No. 5,516,657 (Murphy), and Luckow

(1995).

Issue III. Whether claims 22 and 24 were properly rejected under 35 USC § 103(a) as being obvious over U.S. Patent No. 5, 177,002 (Yamamoto) in view of Cooke (1985), Quirk (1989), U.S. Patent No. 5,652,352 (Lichenstein), U.S. Patent No. 5,516,657 (Murphy), and Luckow (1995), and further in view of Lu (1993).

VII. Argument

Issue I. Whether claim 24 was properly rejected under 35 USC § 112 first paragraph as containing new matter.

The Final Office Action rejects claim 24 under 35 USC § 112, first paragraph as allegedly containing new matter. This rejection is respectfully traversed.

In the 7/11/2005 Amendment, claim 24 was amended to recite the limitation "(c) sequencing the cloned Gc1 peptide, thereby confirming that the cloned Gc1 protein is a cloned wild type Gc1 protein." The Examiner argues that the original specification does not describe or suggest the concept of the sequencing procedure in claim 24, step (c). However, the Specification as filed discloses that Appellant was able to determine, using chemically and proteolytically fragmented Gc, that the smallest domain, domain III contains an essential peptide for macrophage activation (Specification at page 10, lines 5-7). Furthermore, the Haddad reference (Haddad et al. 1992), which was cited in that paragraph and incorporated by reference in its entirety (Specification at page 28, lines 1-2), teaches that it was known in the art to sequence peptides of native serum Gc protein. To be a proper incorporation by reference, it must be set forth in the specification and must: (1) express a clear intent to incorporate by reference by

using the root words "incorporat(e)" and "reference" (e.g., "incorporate by reference"); and (2) clearly identify the referenced patent, application, or publication (37 CFR 1.57). Here, the incorporation of the Haddad reference is shown by the use of that phrase, and the reference is clearly identified, thus the requirements of 37 CFR 1.57 are met.

The Examiner argues that the Specification only refers to the Haddad refernce in regard to vitamin D and actin binding domains of the Gc protein, and that it only refers to chemically and proteolytically fragmented serum (or native) Gc protein. The Examiner further cites portions of Haddad which are seemingly most relevant for construing peptide sequences and argues that this reference only discloses determining the amino-terminal sequence of proteolytic fragments of the Gc protein. The Examiner further argues that the Gc protein sequenced in Haddad, was isolated from its native source and not recombinantly produced. Appellant submits that the relevant portion of Haddad which teaches sequencing of the Gc peptide (also known as DBP) is on p. 7175, column 2, ¶2:

> For peptides correlating with radioactivity in paired gel lanes, their stained membrane bands were isolated with a razor blade and were analyzed for amino-terminal sequence in an Applied Biosystems 473A protein sequencer. **The results obtained were compared with the known sequence of hDBP** (Cooke & David, 1985). [Emphasis added].

Thus Haddad, incorporated entirely into the instant Specification, teaches the sequencing of Gc peptide (i.e., DBP) and comparison to known, wild-type (hDBP) protein. The limitation in claim 24 subsection (c) is directed to sequencing of the Gc protein to determine whether it is wild-type. This is exactly what the Haddad reference shows. The fact that the protein source in

Haddad is natural versus recombinant as in the present application is irrelevant. The Haddad reference teaches sequencing a Gc peptide and comparing it to wild-type, which is what the limitation covers. The Examiner has further argued that the reference only teaches sequencing of a fragment of hDBP. However, chemically (e.g., cyanogen bromide) and proteolytically (e.g., thrombin) fragmented Gcl protein yields overlapping peptides. Sequencing these peptides allows sequencing full-length Gcl protein. These are the standard and well-established procedures for sequencing full-length proteins. Then, Appellant compares the full-length sequenced data of the cloned Gcl protein with the sequence of the full-length protein, as shown in Fig. 3, with known (or native known) Gcl peptide sequence (Cooke & David. J Clin Invest, 1985; 76:2420-24; also see Yamamoto '002). The claim encompasses sequencing by fragments. This limitation is thus not new matter because instead of repeating some information contained in another document, an application incorporates the content of another document or part thereof by reference to the document in the text of the specification. The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed. Replacing the identified material incorporated by reference with the actual text is not new matter. See 37 CFR 1.57 and MPEP § 2163.07.

Accordingly, reconsideration and withdrawal of the rejection of claim 24 under 35 USC § 112 first paragraph is respectfully requested.

Issue II. Whether claim 22 was properly rejected under 35 USC § 103(a).

Claim 22 stands rejected under 35 USC § 103(a) over U.S. Patent No. 5,177,002 (Yamamoto) in view of Cooke (1985), Quirk (1989), U.S. Patent No. 5,652,352 (Lichenstein),

U.S. Patent No. 5,516,657 (Murphy), and Luckow (1995).

To establish a prima facie case of obviousness: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or combination) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), MPEP § 2143. To establish prima facie obviousness, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). MPEP 2143.03.

Here, the Examiner has not established a prima facie case of obviousness because the combined references do not teach or suggest all the limitations of the claim. The claim is drawn to a process for producing a cloned macrophage activating factor (GcMAFc) by cloning a Gcl isoform into a baculovirus vector, expressing the cloned Gcl isoform, and contacting the cloned Gcl protein with immobilized β-galactosidase and sialidase, thus obtaining the cloned macrophage activating factor (GcMAFc). In the '002 patent, Appellant purified native Gc isoform from human blood (plasma) and treated it with immobilized β-galactosidase and sialidase to generate GcMAF. This is in contrast to the claimed method. The method disclosed in the '002 patent only generates GcMAF, not GcMAFc, as in the instantly claimed method. The

'002 patent does not teach or suggest cloning of Gc1, cloning Gc1 in baculovirus vector, or contacting cloned Gc1 with immobilized β-galactosidase and sialidase. The protein disclosed in the '002 patent was not produced by cloning, but by affinity chromatography with human blood. This is an important distinction from the instantly claimed method since the native sequence of the Gc1 protein is critical because when the major Gc isoform (Gcl) is produced in the baculovirus expression system, protein synthesis occasionally yields mutant Gc peptides having amino acid substitutions due to mistakes made during gene transcription and translation. However, Appellant does not use the cloned mutant peptides to produce GcMAFc because the mutant peptides are immunogenic in humans. Thus, only the cloned Gcl protein having the wild type peptide sequence (Figure 3 of the instant application) is used to generate GcMAFc. Thus, the cloned Gc protein has to be sequenced, and have the sequence as shown in Figure 3. Only methods of producing the wild type Gcl peptide synthesized via cloning can produce the GcMAFc, as in the instantly claimed method. Treatment of only the cloned Gc protein with immobilized β-galactosidase and sialidase can generate GcMAFc. These deficiencies are not cured by Cooke. Cooke isolated cDNA and the Gc peptide sequence was deduced from the cDNA but never isolated Gc protein (even non-glycosylated Gc protein).

The Examiner relies on Cooke to teach or suggest that the Gc1 allele can be cloned. However, Cooke does not teach or suggest recombinant expression methods. The Examiner has cited Cooke (1985) for cloning Gc protein via *E. coli*. However, Cooke only cloned cDNA for Gc1 protein and sequenced the cloned cDNA. The amino acid sequence of the entire Gcl protein was deduced from the cloned cDNA sequence (Figs. 2 and 3 of Cooke). Cooke never expressed

Gc protein via the *E. coli* system, thus, Cooke never made the amino acid sequence of Gc protein. Also Cooke never studied the biological activity of the cloned Gc protein because they did not have it: "the primary amino acid sequence of DBP [i.e. Gc protein] was deduced only after DBP cDNAs were cloned and sequenced." (Cooke at 2422, legend to Figure 3, which shows the predicted amino acid sequence of hDBP). Since the Cooke reference teaches the use of prokaryotic vector mediated cloning, any expressed protein would not be glycosylated. This Gc protein has never been used in *in vivo* biological studies. Thus the combination of the '002 patent and the Cooke reference does not teach or suggest a method of cloning Gc1 in baculovirus vector, expression of a cloned Gc1 protein in a baculovirus expression system, or contacting cloned Gc1 expressed in a baculovirus system with immobilized β-galactosidase and sialidase. These deficiencies are not cured by the '352 patent.

The Examiner cites the '352 patent as allegedly showing or suggesting expression of several proteins including Gc protein in insect cells. However, the '352 patent discloses that human afamin, an albumin like protein, can be expressed in insect cells, not Gc1 as in the instantly claimed method. The albumin protein family consists of four serum proteins, albumin, α-fetoprotein, afamin, and vitamin D-binding protein (Gc protein). While they have three structurally similar domains, there are important differences between the family members. The molecular weight of three proteins (i.e., albumin, α-fetoprotein, and afamin) are approximately 87 kDa whereas Gc protein has a smaller molecular weight of 52 kDa. This is because Domain III of Gc protein has a large deletion (equivalent to only 43% of domain III of other albumin family proteins) and thereby the O-glycosylating site (420 threonine residue of Domain III) of

the Gc peptide is available for glycosylation. Appellant teaches that Gc protein is the only O-glycosylated albumin family protein. Gc protein is a membrane-like protein as to O-glycosylation, but is as soluble as a serum protein. O-glycosylation usually occurs in membrane proteins and not in serum proteins. The O-glycosylation of a protein increases solubility and stability of the cloned protein. Since Gc protein is very different from other albumin family proteins, and given the importance of the differences, there is no teaching or suggestion in the '352 patent of the expression and isolation of any and all albumin like proteins, and no teaching or suggestion regarding the specific expression and isolation of Gc1 protein in particular. In contrast, the '352 patent only discloses the expression of afamin in insect cells. Thus, the combination of the '002 patent, the Cooke reference, and the '352 patent does not teach or suggest a method of cloning Gc1 in baculovirus vector, expression of a cloned Gc1 protein in a baculovirus expression system, or contacting cloned Gc1 expressed in a baculovirus system with immobilized β-galactosidase and sialidase. These deficiencies are not cured by the Quirk reference.

While the Quirk reference is directed to producing human serum albumin, it is silent with regard to Gc protein. Quirk et al. cloned and expressed human serum albumin in yeast. Although albumin and Gc protein are in the same family of serum proteins, albumin is a non-glycosylated protein, and differs from Gc1, as set forth above. There is no teaching or suggestion in the Quirk reference regarding the specific expression and isolation of Gc1 protein in particular. Thus the combination of the '002 patent, the Cooke reference, the '352 patent, and the Quirk reference does not teach or suggest a method of cloning Gc1 in baculovirus vector, expression of a cloned

Gc1 protein in a baculovirus expression system, or contacting cloned Gc1 expressed in a baculovirus system with immobilized β-galactosidase and sialidase. These deficiencies are not cured by the '657 Murphy patent and the Luckow reference.

With regard to the recombinant expression of Gc1 in baculovirus, the Examiner relies on the '657 Murphy patent and the Luckow reference, and cites the supposed advantage of baculovirus in the expression of recombinant proteins. However, the only protein that Murphy expressed with this method is the HIV glycoprotein gp120. Unlike the Gc protein, gp120 is not sialylated. There is no evidence in Murphy to suggest that a sialylated protein could be generated as easily due to the nature of protein. The Examiner does not show how or where Luckow teaches or suggests that a baculovirus vector could be successfully employed to express Gc protein in insect cells.

In addition, "[t]here are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. MPEP 2143.01. In the Final Office Action the Examiner admits that the motivation did not come from the prior art references (Final Office Action at 3), thus the motivation must come from the nature of the problem to be solved and the knowledge of persons of ordinary skill in the art. Here, the Examiner argues that the motivation comes from concern

about human viral contamination if Gc is purified from human blood, and that these contaminants may be avoided if these products are obtained via recombinant DNA technology. The Examiner finds further motivation in the alleged advantages of the baculovirus expression system.

However, "[t]o imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." W.L.Gore & Assocs., Inc. v. Garlock, Inc., 220 USPQ 303, 312-13 (Fed. Cir. 1983). Here, the prior art references do not teach or suggest all the, limitations of the claims, and thus the Examiner has used hindsight reasoning in constructing the rejection. Additionally, "[s]kill in the art does not act as a bridge over gaps in the substantive presentation of an obviousness case, but instead supplies the primary guarantee of objectivity in the process." All-Site Corp. v. VSI International Inc., 50 USPQ 1161, 1171 (Fed. Cir. 1999). The Examiner is attempting to substitute skill in the art to act as a bridge over the deficiencies of the teachings of the cited references, since the references themselves do not teach or suggest all the limitations of the claims.

It is the Examiner's position that the combination if the references makes it obvious to practice a method of cloning Gc1 in baculovirus vector, expression of a cloned Gc1 protein in a baculovirus expression system, and contacting cloned Gc1 expressed in a baculovirus system with immobilized β-galactosidase and sialidase. The Examiner's position reflects the "obviousness to try" approach of the "armchair" chemist. Ex parte Maizel, 27 U.S.P.Q.2d 1662

(Bd.Pat.App & Interf.) (1992). In Maizel, the Examiner's rejection of claims for recombinant human B-cell growth factor as obvious in view of prior art, which examiner asserted described protein whose existence would have motivated one skilled in art to isolate protein, sequence it, construct synthetic DNA probes, utilize probes to isolate messenger RNA, synthesize cDNA, and produce additional protein, reflects "obviousness to try" approach of "armchair" chemist, and was reversed. The Board held that the protocol set forth by the examiner would not have been enabling to one of skill in the art. As in Maizel, here there is nothing in the references which teaches or suggests the expression of a properly glycosylated recombinant protein, or that a baculovirus vector could be successfully employed to express Gc protein in insect cells, and as in Maizel, here the protocol set forth by the Examiner would not have been enabling to one of skill in the art.

The Examiner is focusing on the obviousness of substitutions and differences instead of on the invention as a whole, see Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986). In the Hybritech case it was found that an immunometric assay which differed from the prior art by employing monoclonal antibodies bound to a solid carrier (i.e. a so-called sandwich) was patentable despite predictions of the utility of monoclonal antibodies and the fact that sandwich assays were known for polyclonal antibodies. The evidence showed that when monoclonal sandwich assay kits were introduced those skilled in the art were skeptical about their reliability so that their success was not reasonably expected by those skilled in the art. In Hybritech, the mere substitution of monoclonal for polyclonal antibodies in a sandwich assay, was a legally improper way to simplify the difficult determination of obviousness. (Id. at 1383).

Here, the attempt by the Examiner to substitute the baculovirus expression system for isolation of Gc protein from blood by affinity chromatography, when there is nothing in the references which teaches or suggests the expression of a properly glycosylated recombinant protein produced in the baculovirus expression system, or that a baculovirus vector could be successfully employed to express Gc protein in insect cells, is improper.

As set forth above, the Examiner relied on the '657 Murphy patent and the Luckow reference to show the supposed advantage of baculovirus in the expression of recombinant proteins. However, the only protein that Murphy expressed with this method is the HIV glycoprotein gp120. Unlike the Gc protein, gp120 is not sialylated. There is no evidence in Murphy to suggest that a sialylated protein could be generated as easily due to the nature of protein. The Examiner does not show how or where Luckow teaches or suggests that a baculovirus vector could be successfully employed to express Gc1 protein in insect cells. In addition, Gc1 is a secreted protein. Many secreted and membrane proteins produced in the baculovirus expression system frequently form insoluble aggregates or are improperly processed. Furthermore, although post-translational processing in insect cells is more similar to mammalian cells than bacteria and yeast, it is not always identical and, for applications such as therapeutic proteins, this is critical. Improper secretory processing can be especially problematic at several days post-infection when the host cell's post-translational processing machinery has deteriorated. Therefore protein produced in the baculovirus expression system can be poorly processed and be produced as aggregates, and is prone to improper post-translational modifications. In addition, while baculovirus expression systems generally perform post-translational protein modifications

similar to those of mammalian cells, leading to correct secretion and subunit assembly, some recombinant proteins are extensively degraded. Moreover, the vulnerabilities of engineered proteins to proteolytic degradation differ, and the proteolytic activities in different insect cell lines differ as well. The optimal conditions for each case require careful and time-consuming determination. Therefore, given the art recognized difficulties with the baculovirus expression systems, particularly in the production of secreted proteins and post-translationally modified proteins, such as Gc1, a person of ordinary skill in the art would not have been motivated to practice a method of converting Gc1 protein into GcMAFc by contacting the Gc protein with β-GAL and sialidase, wherein the protein had been produced in a baculovirus system.

In addition, while obviousness does not require absolute predictability, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart, 531 F.2d 1048 (CCPA 1976), see also Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1207-08 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success). Here, while the Examiner alleges the advantages of the baculovirus expression system, there are distinct disadvantages to using the baculovirus expression system, because it is prone to misprocessing of secreted proteins. Additionally, in the case of post-translationally modified proteins, as Gc is, the baculovirus system degrades several days after infection, and a large fraction of the recombinant protein will be poorly processed and accumulate as aggregates. The references teach that the optimal conditions for expression of a protein in the baculovirus

expression system require careful and time-consuming determination. Thus, given the teachings of the references that the baculovirus system is prone to misprocessing of secreted proteins and a large fraction of the recombinant protein will be poorly processed and accumulate as aggregates, it would not have obvious to one of skill in the art the time the invention was made to practice a method of cloning a Gc1 isoform into a baculovirus vector because there was not a reasonable expectation of success.

In addition, "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." In re Corkill, 771 F.2d 1496 (Fed. Cir. 1985). Here, there are distinct disadvantages to using the baculovirus expression system, particularly in the case of a secreted and post-translationally modified protein wherein the baculovirus system is prone to misprocessing of such proteins, while Appellant has demonstrated that the baculovirus system unexpectedly produces functional and soluble GcMAFc (see Table 3).

Issue III. Whether claims 22 and 24 were properly rejected under 35 USC § 103(a).

Claims 22 and 24 stand rejected under 35 USC § 103(a) over U.S. Patent No. 5,177,002 (Yamamoto) in view of Cooke (1985), Quirk (1989), U.S. Patent No. 5,652,352 (Lichenstein), U.S. Patent No. 5,516,657 (Murphy), and Luckow (1995), and further in view of Lu (1993). This rejection is respectfully traversed for the reasons set forth below.

The claims are drawn to a process for producing a cloned macrophage activating factor (GcMAFc) by cloning a Gcl isoform into a baculovirus vector, expressing the cloned Gcl isoform, contacting the cloned Gcl protein with immobilized β-galactosidase and sialidase, thus

obtaining the cloned macrophage activating factor (GcMAFc), and further wherein the cloned protein is sequenced. The base references U.S. Patent No. 5,177,002 (Yamamoto), Cooke (1985), Quirk (1989), U.S. Patent No. 5,652,352 (Lichenstein), U.S. Patent No. 5,516,657 (Murphy), and Luckow (1995) have been discussed, *supra*. The combination of the '002 patent, the Cooke reference, the '352 patent, the Quirk reference, the '657 Murphy patent, and the Luckow reference does not teach or suggest a method of cloning Gc1 in baculovirus vector, expression of a cloned Gc1 protein in a baculovirus expression system, or contacting cloned Gc1 expressed in a baculovirus system with immobilized β-galactosidase and sialidase. Additionally, claim 24 is further drawn to sequencing the cloned Gc1 protein, which is also not taught or suggested in the combination of these references. These deficiencies are not cured by the Lu reference.

The Lu reference teaches that to insure high product quality and to evaluate the effectiveness of manufacturing process in removing contaminants and impurities, a series of analytical methods is required to carry out extensive biochemical characterizations and biological analyses of the final purified product (Lu at 465, column 2, first paragraph). However, the Lu reference is silent with regard to cloning Gc1 in baculovirus vector, contacting cloned Gc1 with immobilized β-galactosidase and sialidase, or sequencing Gc1 protein expressed in insect cells. Since all the limitations of the claims are not taught or suggested by the references, the rejection under 35 USC 103(a) is improper.

In addition, as above, while the Examiner alleges the advantages of the baculovirus expression system there are distinct disadvantages to using the baculovirus expression system,

particularly in the case of a secreted protein, *e.g.,* Gc1, wherein the baculovirus system is prone to misprocessing of secreted proteins. Additionally, in the case of post-translationally modified proteins, *e.g.,* Gc1, the baculovirus system degrades several days after infection, and a large fraction of the recombinant protein will be poorly processed and accumulate as aggregates. The references teach that the optimal conditions for expression of a protein in the baculovirus expression system require careful and time-consuming determination. Thus, given the teachings of the references that the baculovirus system is prone to misprocessing of secreted proteins and a large fraction of the recombinant protein will be poorly processed and accumulate as aggregates, it would not have obvious to one of skill in the art the time the invention was made to practice a method of cloning a Gc1 isoform into a baculovirus vector because there was no motivation to combine the references, and there was not a reasonable expectation of success. In addition, the Examiner has further cited the Lu reference. The Lu reference teaches that mistranslation may happen in the production of any recombinant protein, thus this reference weighs against the finding of obviousness. The Lu reference teaches that sequence error at the translational level occurs at a higher frequency (Lu at 471, column 2, first full paragraph) in bacterial expression systems. While the Lu reference teaches bacterial expression systems, the Examiner has cited the reference to stand for the proposition that recombinantly produced proteins should be tested by sequencing after production. This is yet another reason why one of ordinary skill in the art would not have been motivated to practice the claimed method at the time the invention was made, because of the inherent problems with recombinant production of proteins. This is particularly an issue with proteins, as in the protein produced in the instant invention, wherein

the proper amino acid sequence and post-translational modifications are critical.

Lu teaches that in order to insure high product quality and to evaluate the effectiveness of manufacturing process in removing contaminants and impurities, a series of analytical methods is required to carry out extensive biochemical characterizations and biological analyses of the final purified product (Lu at 465, column 2, first paragraph). Thus, given the teachings of the Ailor and Ho references that the baculovirus system is prone to misprocessing of secreted proteins and a large fraction of the recombinant protein will be poorly processed and accumulate as aggregates, and the further teachings of Lu, as cited by the Examiner, that production of proteins by recombinant DNA technology can lead to sequence errors at the translational level, and require a series of analytical methods to carry out extensive biochemical characterizations and biological analyses of the final purified product, the claims are patentable because there is not a motivation to combine the references, and further, there was not a reasonable expectation of success.

Accordingly, reconsideration and withdrawal of the rejection of claims 22 and 24 under 35 USC 103(a) is respectfully requested.

Conclusion

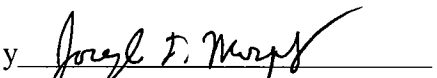
Accordingly, the Honorable Board of Patent Appeals and Interferences is respectfully requested to withdraw the pending rejections and pass this application on to issuance.

The required fee for this Brief, as well as any additional charge or credit, is authorized to be charged to the Deposit Account referenced in the accompanying Form PTO/SB/17.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

November 29, 2006

By 
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VIII. Claims Appendix

Claims 1-21 (Canceled)

22. (Previously Presented) A process for producing a cloned macrophage activating factor (GcMAFc) comprising:

(a) cloning a Gc1 isoform into a baculovirus vector;

(b) expressing the cloned Gc1 isoform, thereby producing a cloned Gc1 protein, wherein the Gc1 protein comprises approximately 458 amino acids with a molecular weight of approximately 52,000 Da and 3 distinct domains;

(c) contacting the cloned Gc1 protein with immobilized beta galactosidase and sialidase; and

(d) obtaining the cloned macrophage activating factor (GcMAFc).

23. (Canceled)

24. (Previously Presented) A process for producing a functional cloned macrophage activating factor (GcMAFc) comprising:

(a) cloning a Gc1 isoform into a baculovirus vector;

(b) expressing the Gc1 isoform, thereby producing a cloned Gc1 protein, wherein the cloned Gc1 protein comprises approximately 458 amino acids with a molecular weight of approximately 52,000 Da and 3 distinct domains;

(c) sequencing the cloned Gc1 peptide, thereby confirming that the cloned Gc1 protein is

a cloned wild type Gc1 protein;

(d) contacting the cloned wild type Gc1 protein in vitro with immobilized beta galactosidase and sialidase, and

(e) obtaining the cloned wild type macrophage activating factor (GcMAFc).

IX. Evidence Appendix

This Appendix contains the following attachment(s):

None

X. Related Proceedings Appendix

This Appendix contains the following attachment(s):

None